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(54) **23-imino derivatives of 23-keto compounds useful as pesticides.**

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Description

BACKGROUND OF THE INVENTION

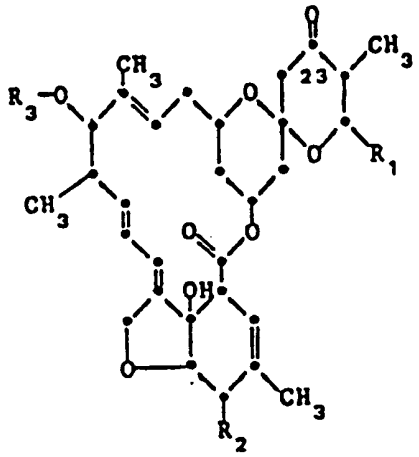
The present invention relates to new 23-imino derivatives of the compounds collectively defined as 23-keto C-076 compounds. These C-076 antibiotics preferably are produced by the fermentation of the microorganism Streptomyces avermitilis. The morphological characteristics, compounds and method for the production of the 23-keto C-076 compounds is disclosed in U.S. Patent 4,289,760, issued to Mrozik et al on September 15, 1981.

The C-076 compounds are complex macrolides which have a 23-hydroxy substituent, as well as two other hydroxy groups. The selective oxidation of this 23-hydroxy group to a 23-oxo group is disclosed. The present invention provides a further derivatization of the oxo group to afford 23-imino derivatives. These 23-imino derivatives of the C-076 compounds are useful for the prevention, treatment or control of helmintic, ectoparasitic, insect, acarid and nematode infections and infestations in warm-blooded animals and agricultural crops.

SUMMARY OF THE INVENTION

The present invention provides novel 23-imino derivatives of the compounds designated 23-keto (or oxo) C-076 compounds.

The 23-keto C-076 compounds have the following structural formula:



wherein,

R_1 is isopropyl or sec-butyl;

R_2 is methoxy, hydroxy, lower alkanoyloxy or substituted lower alkanoyloxy wherein the substituent is hydroxy, carboxy, phenoxy or mono-, di- or tri-halo such as trifluoroacetyl, trichloroacetyl, chloroacetyl and the like; and

R_3 is hydrogen, α-L-oleandrosyl, 4′-(α-L-oleandrosyl)-α-L-oleandrosyl, 4″-lower alkanoyl-4′-(α-L-oleandrosyl)-α-L-oleandrosyl, or 4″(substituted lower alkanoyl)-4′-(α-L-oleandrosyl)-α-L-oleandrosyl wherein the substituent is hydroxy, carboxy, phenoxy or mono-, di, or tri-halo such as trifluoroacetyl, trichloroacetyl, chloroacetyl and the like.

The compounds of the present invention are useful anthelmintics, ectoparasiticides, insecticides, acaricides and nematicides in treating, preventing or controlling such diseases in warm-blooded animals, such as poultry, cattle, sheep, swine, rabbits, horses, dogs, cats and human beings and agricultural crops.

Although these diseases have been recognized for years and therapies exist for the treatment and prevention of the diseases, the present invention provides novel compounds in the search for effective such therapy.

U.S. Patent 3,950,360, Aoki et al, April 13, 1976 discloses certain antibiotic substances obtained by culturing a Streptomyces microorganism, said compounds being useful as insecticides and acaricides. Further, an entire series of U.S. patents relates to certain compounds produced by the fermentation of Streptomyces avermitilis (U.S. Patent 4,171,314, Chabala et al, October 16, 1979; U.S. Patent 4,199,569,

Chabala et al, April 22, 1980; U.S. Patent 4,206,205, Mrozik et al, June 3, 1980; U.S. Patent 4,310,519, Albers-Schonberg, January 12, 1982; U.S. Patent 4,333,925, Buhs et al, June 8, 1982). U.S. Patent 4,423,209, Mrozik, December 27, 1983 relates to the process of converting some of these less desirable components to more preferred ones. Finally, British Patent Application No. 2166436 A discloses antibiotics also.

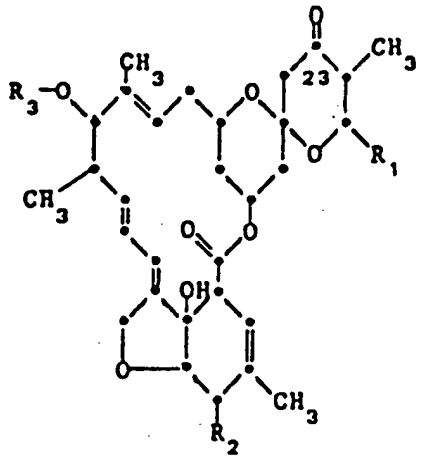
The present compounds or the pharmaceutically and pharmacologically acceptable salts thereof exhibit excellent and effective treatment, prevention and/or control of these serious diseases of warm-blooded animals.

It is an object of the present invention, therefore, to provide novel 23-imino derivatives of 23-keto C-076 compounds. It is a further object to provide a process for the preparation of these derivatives and to provide methods for preventing, treating or controlling endo and ectoparasitic (collectively parasitic), insect, nematode, acarid and helmintic diseases in warm-blooded animals and agricultural crops by providing compositions containing prophylactically, therapeutically or pharmaceutically-effective amounts of the present novel compounds.

These and other objects of the invention will become apparent by the more detailed description of the invention provided hereinbelow.

DETAILED DESCRIPTION OF THE INVENTION

The 23-keto C-076 compounds which may act as precursors of the present compounds are represented by the following structural formula,



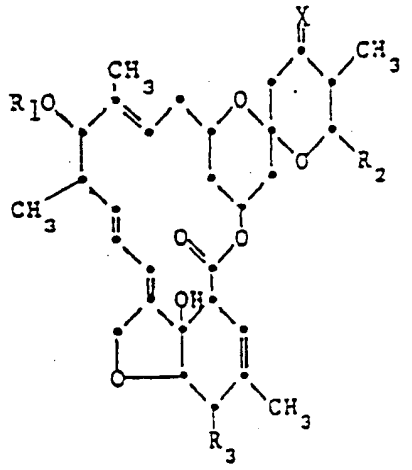
wherein,

R_1 is isopropyl or sec-butyl;

R_2 is methoxy, hydroxy, lower alkanoyloxy or substituted lower alkanoyloxy wherein the substituent is hydroxy, carboxy, phenoxy or mono-, di- or tri-halo such as trifluoroacetyl, trichloroacetyl, chloroacetyl and the like; and

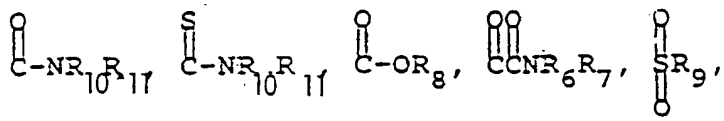
R_3 is hydrogen, α-L-oleandrosyl, 4′-(α-L-oleandrosyl)-α-L-oleandrosyl, 4″-lower alkanoyl-4′-(α-L-oleandrosyl)-α-L-oleandrosyl, or 4″(substituted lower alkanoyl)-4'-(α-L-oleandrosyl)-α-L-oleandrosyl wherein the substituent is hydroxy, carboxy, phenoxy or mono-, di, or tri-halo such as trifluoroacetyl, trichloroacetyl, chloroacetyl and the like.

The compounds of the instant invention are represented by the following structural formula:

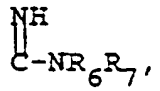


wherein,

R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl or α-L-oleandrosyl; R_2 is isopropyl or sec-butyl; R_3 is methoxy, hydroxy, acetoxy, methoxyacetoxy or chloroacetoxy; X is NOR_4, or N-NHR_5; R_4 is C_1-C_4 alkoxymethyl, CH_2COO-alkyl (C_1-C_4), N-(allyl) carbamoyl, N-(propargyl)-carbamoyl, phenylacetyl substituted on the phenyl ring with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, phenoxy-acetyl optionally substituted on the phenyl ring by one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, or benzoyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_5 is



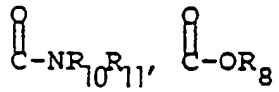
C_1-C_6 alkanoyl, formyl, C_1-C_6 alkyl,



benzoyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_6 and R_7 are hydrogen, C_1-C_6 alkyl, or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_8 is C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_9 is C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_{10} and R_{11} are hydrogen, C_{1-6} alkyl or phenyl optionally subsituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, with the proviso that both R_{10} and R_{11} are not hydrogen at the same time; and the pharmaceutically and pharmaceutically acceptable salts thereof.

A preferred group of compounds of structure (I) is defined by

X, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11}	as defined hereinabove; and
R_3	as hydroxy or methoxy, wherein
X	is N-NHR_5; wherein
R_5	is



or C_1-C_6 alkyl;

R_2 is isopropyl or sec-butyl;

R_3 is hydroxy; and

R_1, R_8 R_{10} and R_{11} are as defined hereinabove.

The most preferred group of compounds of structure (I) is where

X is NOR_4 or N-NHR_5

R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl.

R_2 is isopropyl or sec-butyl;

R_3 is hydroxy;

R_4 is C_1-C_6 alkyl; and

R_5 is

The imino derivatives of the 23-keto (oxo) compounds are readily prepared by standard techniques such as procedures described by S. M. McElvain in The Characterization of Organic Compounds, published by MacMillan Company, New York, 1953, pages 204-205.

Typically, a 23-oxo compound is stirred in alcohol, such as methanol or ethanol, or dioxane in the presence of acetic acid and an excess of the amino derivatizing agent, such as hydroxylamine hydrochloride, methoxyamine hydrochloride, semicarbazide hydrochloride and the like along with an equivalent amount of sodium acetate, at room temperature (25 °C) to 50 °C. The reaction is usually complete in several hours to several days at room temperature but can be readily speeded by heating.

The compounds of structure (I) wherein X is NOR_4 and R_4 is C_1-C_6 alkoxycarbonyl, chloroacety, methoxyacety, phenylacety, C_1-C_6 alkyl-NHCO, are prepared by treating the structure (I) compounds, wherein X is NOH, with acid anhydrides or isocyanates. The reactions are conducted in inert solvents, such as methylene chloride, ethylene dichloride or dioxane, in the presence of a tertiary amine such as triethylamine or diisopropylethylamine. Generally, the reactions are conducted from 0 °C to room temperature (25 °C), but if the reactions are sluggish, heat is applied. An equivalent to a slight excess of the acid anhydride is used to avoid reaction at the 5- or 4″-hydroxy groups.

The novel compounds of the present invention have significant activity as anthelmintics, ectoparasiticides, insecticides, nematicides and acaricides in human and animal health areas and in agriculture.

The disease or group of diseases described generally as helminthiasis is due to infection of an animal host with parasitic worms known as helminths. Helminthiasis is a prevalent and serious economic problem in domesticated animals such as swine, sheep, horses, cattle, goats, dogs, cats and poultry. Among the helminths, the group of worms described as nematodes causes widespread and often times serious infection in various species of animals. The most common genera of nematodes infecting the animals referred to above are Haemonchus, Trichostrongylus, Ostertagia, Nematodirus, Cooperia, Ascaris, Bunostomum, Oestophagostomum, Chabertia, Trichuris, Strongylus, Trichonema, Dictyocaulus, Capillaria, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancylostoma, Uncinaria, Toxascaris and Paracaris. Certian of these, such as Nematodirus, Cooperia, and Oesphagostomum primarily attack the intestinal tract while others, such as Haemonchus and Ostertagia, are most prevalent in the stomach. Still others such as Dictyocaulus are found in the lungs. Also, other parasites may be located in other tissues and organs of the body such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like. The parasitic infections known as helminthiases lead to anemia, malnutrition, weakness, weight loss, severe damage to the walls of the intestinal tract and other tissues and organs, and if left untreated, may result in death of the infected host. The 23-imino derivatives of the 23-keto C-076 compounds of this invention unexpectedly have high activity against these parasites. Additionally, they also are active against Dirofilaria in dogs, Nematospiroides, Syphacia, Aspiculuris in rodents, arthropod ectoparasites such as ticks, mites, lice, fleas, blowfly of animals and birds, the ectoparasite Lucilia sp. of sheep, biting insects and migrating dipterous larvae such as Hypoderma sp. in cattle, Gastrophilus in horses and Cuterebra sp. in rodents.

The compounds of the present invention also are useful in treating, preventing or controlling parasites which infect human beings, as well. The most common genera of parasites of the gastrointestinal tract of man are Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Trichuris, and Enterobius. Other medically important genera of parasites which are found in the blood or other tissues and organs outside the gastrointestinal tract are the filiarial worms such as Wuchereria, Brugia, Onchocerca and Loa, Dracunculus and extra-intestinal stages of the intestinal worms Strongyloides and Trichinella. The present compounds also are of value against arthropods parasitizing man, biting insects and other dipterous pests causing annoyance to man.

These compounds further are active against household pests such as the cockroach, Blattella sp., clothes moth, Tineola sp., carpet beetle, Attagenus sp., and the housefly Musca domestica.

Insect pests of stored grains such as Tribolium sp., Tenebrio sp., and of agricultural plants such as spider mites (Tetranycus sp.), southern army worms, tobacco budworms, boll weevils, aphids (Acyrthiosiphon sp.), migratory orthopterans such as locusts and immature stages of insects living on plant tissue are controlled by the present compounds as well as the control of soil nematodes and plant parasites such as Meloidogyne sp., which may be of importance in agriculture.

The compounds of the present invention may be administered orally or parenterally for animal and human usage, while they may be formulated in liquid or solid form for agricultural use. Oral administration may take the form of a unit dosage form such as a capsule, bolus or tablet, or as a liquid drench where used as an anthelmintic for animals.

The animal drench is normally a solution, suspension or dispersion of the active compound, usually in water, together with a suspending agent such as bentonite and a wetting agent or like excipient. Generally, the drenches also contain an antifoaming agent. Drench formulations generally contain about 0.001% to 0.5%, by weight, of the active compound. Preferred drench formulations contain about 0.01% to 0.1% by weight.

Capsules and boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate or di-calcium phosphate.

Where it is desired to administer the 23-imino derivatives of C-076 in a dry, solid unit dosage form, capsules, boluses or tablets containing the desired amount of active compound usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be varied widely with respect to their total weight and content of the active compound depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the active compound is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top dressing or in the form of pellets which may then be added to the finished feed or optionally fed separately. Alternatively, the active compounds of the present invention may be administered to animals parenterally, such as by intraruminal, intramuscular, intratracheal, or subcutaneous injection. In such an event, the active compound is dissolved or dispersed in a liquid carrier vehicle.

For parenteral administration, the active compound is suitable admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cotton seed oil and the like. Other parenteral vehicles such as organic preparations using solketal, propylene glycol, glycerol formal, and aqueous parenteral formulation also are used. The active 23-imino compound or compounds of the present invention are dissolved or suspended in the parenteral formulation for administration. Such formulations generally contain about 0.005% to 5%, by weight, of the active compound.

Although the compounds of the present invention are primarily uses in the treatment, prevention or control of helminthiasis, they also are useful in the prevention and treatment of diseases caused by other parasites. For example, arthropod parasites such as ticks, lice, fleas, mites and other biting insects in domesticated animals and poultry are controlled by the present compounds. These compounds also are effective in treatment of parasitic diseases that occur in other animals including human beings. The optimum amount to be employed will, of course, depend upon the particular compound employed, the species of animal to be treated and the type and severity of parasitic infection or infestation. Generally, the amount useful in oral administration of these novel compounds is about 0.001 mg to 10 mg per kg of animal body weight, such total dose being given at one time or in divided doses over a relatively short period of time (1-5 days). The preferred compounds of the invention give excellent control of such parasites in animals by administering about 0.025 mg to 3 mg per kg of animal body weight in a single dose. Repeat treatments are given as required to combat re-infections and are dependent upon the species of parasite and the husbandry techniques being employed. The techniques for administering these materials to animals are known to those skilled in the veterinary field.

When the compounds described herein are administered as a component of the animal's feed, or dissolved or suspended in the drinking water, compositions are provided in which the active compound or compounds are intimately dispersed in an inert carrier or diluent. An inert carrier is one that will not react with the active component and that will be administered safely to animals. Preferably, a carrier for feed administration is one that is, or may be, an ingredient of the animal ration.

Suitable compositions include feed premixes or supplements in which the active compound is present in relatively large amounts, wherein said feed premixes or supplements are suitable for direct feeding to the animal or for addition to the feed either directly or after an intermediate dilution or blending step.

Typical carriers or diluents suitable for such compositions include distillers' dried grains, corn meal, citrus meal, fermentation residues, ground oyster shells, wheat shorts, molasses solubles, corn cob meal, edible bean mill feed, soya grints, crushed limestone and the like. The active compounds are intimately dispersed throughout the carrier by methods such as grinding, stirring, milling or tumbling. Compositions containing about 0.005% to 2.0%, by weight, of the active compound are particularly suitable as feed premixes.

Feed supplements, which are fed directly to the animal, contain about 0.0002% to 0.3%, by weight, of the active compounds. Such supplements are added to the animal feed in an amount to give the finished feed the concentration of active compound desired for the treatment, prevention and/or control of parasitic diseases. Although the desired concentration of active compound will vary depending upon the factors previously mentioned as well as upon the particular derivative employed, the compounds of this invention are usually fed at concentrations of about 0.00001% to 0.02% in the feed in order to achieve the desired antiparasitic result.

The compounds also may be administered by pouring on the skin of animals via a solution. Generally, the active compounds are dissolved in a suitable inert solvent, such as dimethylsulfoxide, propylene glycol of the like, alternatively in combination of solvents, for the pour-on administration.

The compounds of this invention also are useful in combating agricultural pests that inflict damage upon growing or stored crops. The present compounds are applied, using known techniques such as sprays, dusts, emulsions and the like, to the growing or stored crops to effect protection from such agricultural pests.

The present invention is illustrated by the following examples which are illustrative of said invention and not limitative thereof.

EXAMPLES 1 AND 2

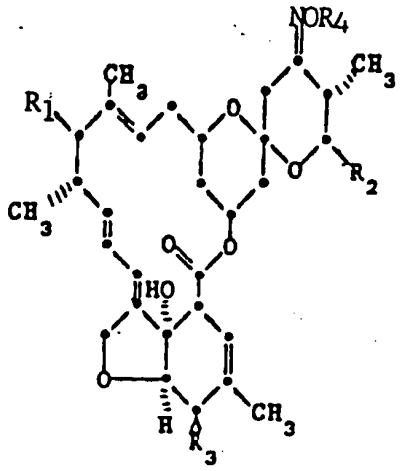
23-Methoxime-C-076-B2a

In 54 mL of dry dioxane, 89 mg of 23-keto-C-076-B2a is stirred with 64 mg of $MeONH_2 \cdot HCl$, 63 mg of NaOAc and 11 mL of HOAc for 24 hours. The mixture is poured into 200 mL each of CH_2Cl_2 and H_2O, and the layers are separated. The aqueous layer is further extracted with 50 mL of CH_2Cl_2 and the combined CH_2Cl_2 extracts are washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. The crude product is purified by preparative layer chromatography (silica gel) using 5% MeOH in CH_2Cl_2 to afford the title compound, that is identified by mass spectrometry and NMR spectroscopy.

The 23-methoxime-C-076-B2b is prepared similarly.

EXAMPLES 3-15

In the manner described in Examples 1 and 2, the following compounds are prepared by substituting the appropriate O-substituted hydroxylamine hydrochloride for $MeONH_2 \cdot HCl$, as needed, and purifying the products by chromatograph on silica gel. The products are identified by mass spectroscopy and NMR spectroscopy.



R_1 = 4'-(α-L-oleandrosyl)-α-L-oleandrosyloxy.

R_4	R_2	R_3
$C_2H_5OCOCH_2$	sec-butyl	OH
C_2H_5	sec-butyl	OH
H	sec-butyl	OH
n-C_3H_7	sec-butyl	OH
i-C_3H_7	sec-butyl	OH
n-C_6H_{13}	sec-butyl	OH
Propargyl-	sec-butyl	OH
Allyl-	sec-butyl	OH
Benzyl-	sec-butyl	OH
C_2H_5	i-propyl	OCH_3
C_2H_5	sec-butyl	OCH_3
Phenyl-	sec-butyl	OH
H	i-propyl	OH

EXAMPLE 16

4", 5-Di-O-(t-Butyldimethylsilyl)-23-oxime-C-076-B2a

In the manner described in Examples 1 and 2, 4", 5-di-O-(t-butyldimethylsilyl)-23-keto-C-076-B2a is treated with $NH_2OH \cdot HCl$ to afford the title product. Purification is completed by chromatography on silica gel, and the title compound is characterized by mass spectrometry and NMR spectroscopy.

EXAMPLE 17

23-[O-(Methylcarbamoyl)oxime]-C-076-B2a

In 5 mL of Et_2O, 35 mg of 4", 5-di-O-(t-butyldimethylsilyl)-23-oxime-C-076-B2a is stirred under N_2 with 10 µl of Et_3N and 50 µL of methyl isocyanate for 24 hours at room temperature. The ether is evaporated, and the residue is purified on a preparative chromatograpic plate (silica gel) using 5% MeOH in CH_2Cl_2. The product is then dissolved in 2 mL of MeOH containing p-toluenesulfonic acid $\cdot H_2O$ (2 mole equivalents) and stirred for 0.5 hours. Then, EtOAc is added, and the solution is washed with $NaHCO_3$ solution and H_2O (3 x 2 ml) and dried (Na_2SO_4). Removal of solvents affords the title compound that is identified by mass spectrometry and NMR spectroscopy.

EXAMPLE 18

4", 5-Di-O-(t-Butyldimethylsilyl)-23-keto-C-076-B2a

In 5 mL of DMF containing 0.5 g of 23-keto-C-076-B2a, 250 mg of imidazole is added followed by 250 mg of t-butyldimethylsilyl chloride. The reaction mixtures is stirred under N_2 for 3 hours at 15°C, and 75 mL of Et_2O and 25 mL of H_2O are added. The layers are separated, and the aqueous layer is extracted further with Et_2O. The combined Et_2O layers are washed with H_2O several times, dried (M_9SO_4) and evaporated to dryness. The residue is purified by preparative layer chromatography using 5% MeOH in CH_2Cl_2. The title compound is identified by mass spectrometry and NMR spectroscopy.

EXAMPLE 19

23-[O-(Acetyl)oxime]-C-076-B2a

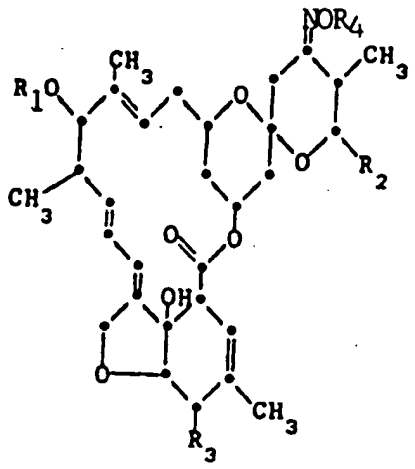
In 0.5 mL of pyridine, 25 mg of 4", 5-di-O(t-butyldimethylsilyl)-23-oxime-C-076-B2a is stirred at 0°C while 0.05 mL of Ac_2O is added. The mixture is allowed to stir at room temperature for 2 hours and poured into ice-water. The mixture is extracted with CH_2Cl_2, and the extract is washed with 5% $NaHCO_3$ solution. After drying (Na_2SO_4), the CH_2Cl_2 is evaporated to dryness and the residue is dissolved in 2 mL of MeOH and stirred with 20 mg of p-toluenesulfonic acid hydrate at 15°C for 0.5 hours. The mixture is diluted with 5 mL of CH_2Cl_2, and the solution is washed with dilute $NaHCO_3$ solution and water. The solution is dried (Na_2SO_4) and chromatographed over silica gel using 2% MeOH in CH_2Cl_2 to afford the title compound that is identified by mass spectrometry and NMR spectroscopy.

The title compound also is prepared by dissolving 100 mg of 23-oxime-C-076-B2a in 3 mL of CH_2Cl_2 containing 52 mg of diisopropylethylamine and adding 25 mg of acetic anhydride in 0.5 mL of Ch_2Cl_2 at 0°C. After an hour, the mixture is quenched with ice, extracted with CH_2Cl_2, and the CH_2Cl_2 solution is evaporated to dryness. The crude product is then purified by chromatography in the manner described hereinabove to afford the title compound.

EXAMPLE 20-26

23-[O-(substituted)oxime]-C-076-Compounds

In the manners described in Example 19, the following compounds are prepared by using the requisite acid anhydride with appropriate 23-oxime-C-076 compounds



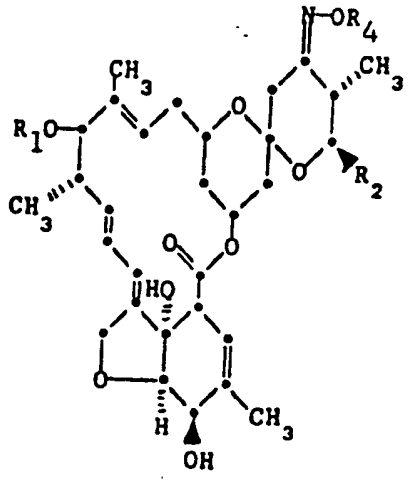
R_1	R_2	R_3
$ClCH_2CO$	sec-butyl	OH
CH_3OH_2CO	sec-butyl	OH
n-C_3H_7CO	sec-butyl	OH
benzyl-CO	sec-butyl	OH
benzoyl-	sec-butyl	OH
CH_3OCH_2CO	i-propyl	OH
CH_3OCH_2CO	sec-butyl	CH_3O

and R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl.

EXAMPLES 27-37

23-[O-(N-substituted carbamoyl)oxime]-C-076-B2a (or B2b) Compounds

In the manner described in Example 17, the following 23-O-(N-substituted carbamoyl)oximes of C-076 compounds are prepared by using the appropriate isocyanates and 4'', 5-di-O-(t-butyldimethylsilyl)-23-oxime-C-076-B2a (or B2b) compounds:



R_4	R_2
C_2H_5NCO	sec-butyl
i-C_3H_7NHCO	sec-butyl
n-$C_6H_{13}NHCO$	sec-butyl
Benzyl-NHCO	sec-butyl
Phenyl-NHCO	sec-butyl
3,4-Dichlorophenyl-NHCO	sec-butyl
4-Chlorophenyl-NHCO	sec-butyl
Allyl-NH-CO	sec-butyl
Propargyl-NH-CO	sec-butyl
C_2H_5NHCO	i-propyl
CH_3NHCO	i-propyl

and R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl.

EXAMPLES 38-39

23-Methoxime-C-076-B2a-4", 5-di-O-Acetate

By the procedure described in Examples 1 and 2, 23-keto-C-076-B2a-4", 5-di-O-acetate is reacted with $MeONH_2 \cdot HCl$ to afford the title compound that is purified over silica gel and identified by mass spectrometry and NMR spectroscopy.

Similarly, the 23-methoxime-C-076-B2a-5-O-acetate is prepared in the above manner from its corresponding ketone.

EXAMPLE 40

23-Methoxime-C-076-B2a-4″, 5-di-O-chloroacetate

In the manner described in Examples 1 and 2, 23-keto-C-076-B2a-4″, 5-di-O-chloroacetate is converted into the title compound. This is then purified by chromatography over silica gel and identified by mass spectral analysis and NMR spectroscopy.

EXAMPLES 41-47

23-(2-Carbomethoxyhydrazone)-C-076-B2a

In 15 mL of MeOH, 50 mg of 23-keto-C-076-B2a is stirred with 25 mg of methyl carbazate in the presence of 10 µL of HOAc. After 3 days, the mixture is poured on ice and diluted with H_2O. The aqueous phase is saturated with sale, and then is extracted CH_2Cl_2 several times. The extracts are dried (Na_2SO_4) and evaporated to dryness. The residue is chromatographed on silica gel using 2% isopropanol in CH_2Cl_2 as eluent to afford the title compound.

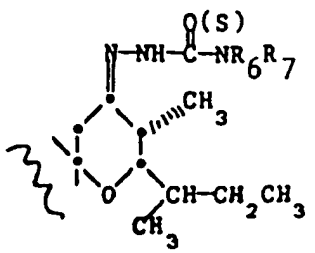
In the same manner, the 2-carbethoxyhydrazone and 2-carbobutoxyhydrazones are prepared using the corresponding carbazates. The 2-carbomethoxyhydrazone and 2-carbethoxyhydrazones of 13-deoxy-23-oxo-C-076-B2a-aglycone are also prepared in the same manner. Also 1-methylhydrazine and acethydrazide are substituted for methylcarbazate to afford 23-(1-methylhydrazone)-C-076-B2a and 23-(acethydrazone)-C-076-B2a, respectively.

EXAMPLES 48-55

23-Semicarbazide-C-076-B2a

In the manner described in Examples 1 and 2, semicarbazide hydrochloride is substituted for $MeONH_2 \cdot HCl$, and the reaction mixture is stirred for 6 days to afford the title compound after purification by chromatography.

Similarly, the semicarbazone and thiosemicarbazone of 13-deoxy-23-oxo-C-076-B2a-aglycone are prepared from the corresponding N-substituted thiosemicarbazides and semicarbazides.



(partial structure)
of C-076-B2a

R_6	R_7
CH_3	H
CH_3	CH_3
n-C_4H_9	H
CH_3	H (thiosemicarbazone)
CH_3	CH_3 (thiosemicarbazone)

EXAMPLES 56-59

Imino Derivatives of 23-Keto-C-076-B2a-Monosaccaride

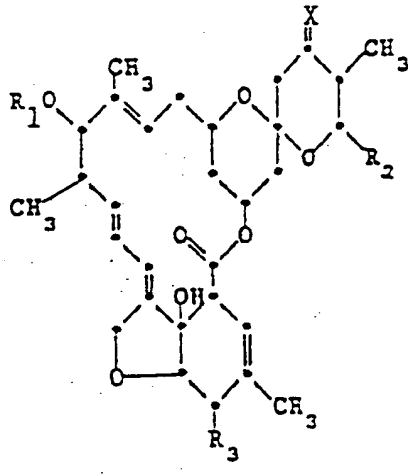
The following 23-imino derivatives of 23-keto-C-076-B2a-monosaccaride are prepared using the methods in the Examples specified:

23-Methoxime	Examples 1 and 2
23-Semicarbazone	Examples 48-55
23-(1-Methylhydrazone)	Examples 41-47
23-Acethydrazone	Examples 41-47

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, FR, GB, GR, IT, LU, NL, SE

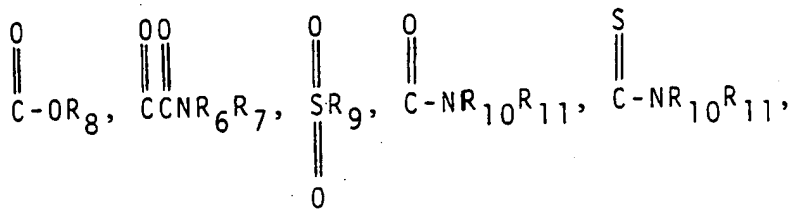
1. The compounds characterized by the structural formula (I):



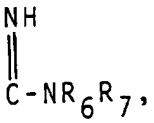
(I)

wherein

R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl or α-L-oleandrosyl; R_2 is isopropyl or sec-butyl; R_3 is methoxy, hydroxy, acetoxy, methoxyacetoxy or chloroacetoxy; X is NOR_4 or $N\text{-}NHR_5$; R_4 is C_1-C_4 alkoxymethyl, CH_2COO-alkyl (C_1-C_4), N-(allyl)carbamoyl, N-(propargyl)carbamoyl, phenylacetyl substituted on the phenyl ring with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, phenoxyacetyl optionally substituted on the phenyl ring by one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, or benzoyl substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_5 is

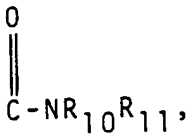


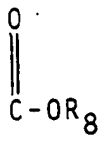
C_1-C_6 alkanoyl, C_1-C_6 alkyl,



benzoyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_6 and R_7 are hydrogen, C_1-C_6 alkyl, or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, R_8 is C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, R_9 is C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_{10} and R_{11} are hydrogen, C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, with the proviso that both R_{10} and R_{11} are not hydrogen at the same time; and the pharmaceutically and pharmacologically acceptable salts thereof.

2. A compound according to Claim 1, wherein R_3 is hydroxy or methoxy and X, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are as described in said Claim 1; wherein X is N-NHR$_5$; R_5 is





or C_1-C_6 alkyl; R_2 is isopropyl or sec-butyl; R_3 is hydroxy; and R_1, R_8, R_{10} and R_{11} are as defined in said Claim 1.

3. A method for controlling plant insects topically or systemically, and protecting crops, trees, shrubs, stored grain and ornamentals, said method characterized by: applying an insecticidally effective amount of the compound represented by structural formula (I), as defined in Claim 1, and the pharmaceutically and pharmacologically acceptable salts thereof.

4. A method according to Claim 3, wherein in said compound X is $NOCH_3$; R_2 is sec-butyl; R_3 is hydroxy; and R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl.

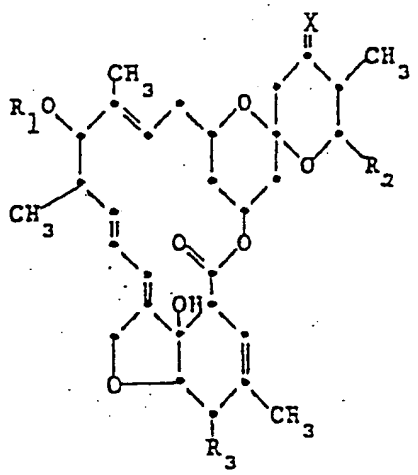
5. A method for the control of plant nematodes, said method characterized by: applying to the foilage of plants, the soil in which they are grown or into the trunks thereof, a nematicidally effective amount of the compound represented by structural formula (I) as defined in Claim 1, and the pharmaceutically and pharmacologically acceptable salts thereof.

6. A composition for use in the treatment, prevention or control of endo- and/or ectoparasitic infections in warm-blooded animals, said composition characterized by: a prophylactically, therapeutically or pharmaceutically effective amount of the compound represented by structural formula (I) as defined in Claim 1 and the pharmaceutically and pharmacologically acceptable salts thereof; and an inert solid or liquid carrier therefor.

7. A composition for controlling insects, said composition characterized by: an insecticidally effective amount of the compound represented by the structural formula (I) as defined in Claim 1 and the pharmaceutically and pharmacologically acceptable salts thereof; and an inert solid or liquid carrier therefor.

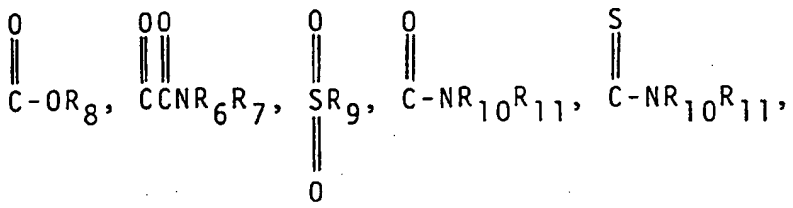
Claims for the following Contracting State : ES

1. A process for preparing compounds characterized by the structural formula (I):

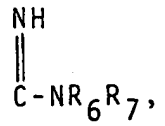


(I)

wherein
R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl or α-L-oleandrosyl; R_2 is isopropyl or sec-butyl; R_3 is methoxy, hydroxy, acetoxy, methoxyacetoxy or chloroacetoxy; X is NOR_4 or $N\text{-}NHR_5$; R_4 is C_1-C_4 alkoxymethyl, CH_2COO-alkyl (C_1-C_4), N-(allyl)carbamoyl, N-(propargyl)carbamoyl, phenylacetyl substituted on the phenyl ring with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, phenoxyacetyl optionally substituted on the phenyl ring by one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, or benzoyl substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_5 is

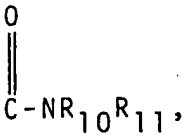


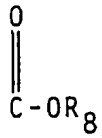
C_1-C_6 alkanoyl, C_1-C_6 alkyl,



benzoyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_6 and R_7 are hydrogen, C_1-C_6 alkyl, or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, R_8 is C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_9 is C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups; R_{10} and R_{11} are hydrogen, C_1-C_6 alkyl or phenyl optionally substituted with one or two halogens, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or nitro groups, with the proviso that both R_{10} and R_{11} are not hydrogen at the same time; and the pharmaceutically and pharmacologically acceptable salts thereof, said process comprising a conversion of the 23-keto (oxo) compounds into the imino derivatives by standard techniques, wherein a 23-oxo-compound is stired in alcohol or dioxan in the presence of acetic acid and an excess of the amino derivatizing agent along with an equivalent amount of sodium acetate, at room temperature to 50 °C, and wherein the compounds of structure (I) wherein X is NOR_4 and R_4 is C_1-C_6 alkoxycarbonyl, chloroacety, methoxyacety, phenylacety, C_1-C_6 alkyl-NHCO, are prepared by treating the structure (I) compounds, wherein X is NOH, with acid anhydrides or isocyanates in an inert solvent in the presence of a tertiary amine at a temperature from 0 °C to room temperature or with application of heat.

2. A process according to Claim 1, wherein R_3 is hydroxy or methoxy and X, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are as described in said Claim 1; wherein X is N-NHR_5; R_5 is





or C_1-C_6 alkyl; R_2 is isopropyl or sec-butyl; R_3 is hydroxy; and R_1, R_8, R_{10} and R_{11} are as defined in said Claim 1.

3. A method for controlling plant insects topically or systemically, and protecting crops, trees, shrubs, stored grain and ornamentals, said method characterized by: applying an insecticidally effective amount of the compound represented by structural formula (I), as defined in Claim 1, and the pharmaceutically and pharmacologically acceptable salts thereof.

4. A method according to Claim 3, wherein in said compound X is $NOCH_3$; R_2 is sec-butyl; R_3 is hydroxy; and R_1 is 4'-(α-L-oleandrosyl)-α-L-oleandrosyl.

5. A method for the control of plant nematodes, said method characterized by: applying to the foilage of plants, the soil in which they are grown or into the trunks thereof, a nematicidally effective amount of the compound represented by structural formula (I) as defined in Claim 1, and the pharmaceutically and pharmacologically acceptable salts thereof.

6. A composition for use in the treatment, prevention or control of endo- and/or ectoparasitic infections in warm-blooded animals, said composition characterized by: a prophylactically, therapeutically or phar-

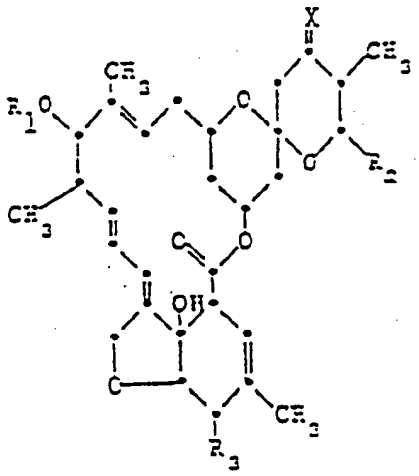
maceutically effective amount of the compound represented by structural formula (I) as defined in Claim 1 and the pharmaceutically and pharmacologically acceptable salts thereof; and an inert solid or liquid carrier therefor.

7. A composition for controlling insects, said composition characterized by: an insecticidally effective amount of the compound represented by the structural formula (I) as defined in Claim 1 and the pharmaceutically and pharmacologically acceptable salts thereof; and an inert solid or liquid carrier therefor.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, FR, GB, GR, IT, LU, NL, SE

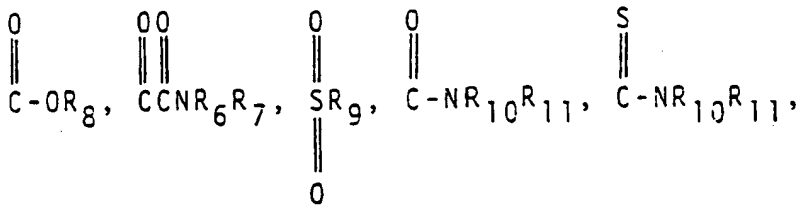
1. Verbindungen, gekennzeichnet durch die allgemeine Strukturformel (I):



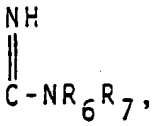
(I)

worin

R_1 4'-(α-L-Oleandrosyl)-α-L-oleandrosyl oder α-L-Oleandrosyl ist; R_2 Isopropyl oder sec-Butyl ist; R_3 Methoxy, Hydroxy, Acetoxy, Methoxyacetoxy oder Chloroacetoxy ist; X NOR_4 oder N-NHR_5 ist; R_4 C_1-C_4-Alkoxymethyl, CH_2COO-Alkyl (C_1-C_4), N-(Allyl)carbamoyl, N-(Propargyl)carbamoyl, Phenylacetyl, substituiert am Phenylring mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, Phenoxyacetyl, wahlweise substituiert am Phenylring mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen oder Benzoyl, wahlweise substituiert mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_5

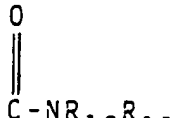


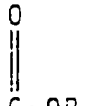
C_1-C_6-Alkanoyl, Formyl, C_1-C_6-Alkyl,



Benzoyl, wahlweise substituiert mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_6 und R_7 Wasserstoff, C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, sind; R_8 C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_9 C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_{10} und R_{11} Wasserstoff, C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist, vorausgesetzt, daß R_{10} und R_{11} nicht gleichzeitig beide Wasserstoff sind; und die pharmazeutisch und pharmakologisch verträglichen Salze davon.

2. Verbindung gemäß Anspruch 1, worin R_3 Hydroxy oder Methoxy ist und X, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} und R_{11} wie in
besagtem Anspruch 1 sind; worin X N-NHR_5 ist; R_5





oder C_1-C_6 Alkyl ist; R_2 Isopropyl oder sec-Butyl ist; R_3 Hydroxy ist; und R_1, R_8, R_{10} und R_{11} wie in besagtem Anspruch 1 definiert sind.

3. Verfahren zur topischen oder systemischen Bekämpfung von Pflanzeninsekten und zum Schutz von Ernten, Bäumen, Sträuchern, gelagertem Getreide und Zierpflanzen, besagtes Verfahren, dadurch gekennzeichnet, daß eine insektizid wirksame Menge der Verbindung, dargestellt durch Strukturformel (I), wie in Anspruch 1 definiert, und die pharmazeutisch und pharmakologisch verträglichen Salze davon angewendet werden.

4. Verfahren gemäß Anspruch 3, worin in besagter Verbindung X $NOCH_3$ ist; R_2 sec-Butyl ist; R_3 Hydroxy ist; und R_1 4'-(α-L-Oleandrosyl)-α-L-oleandrosyl ist.

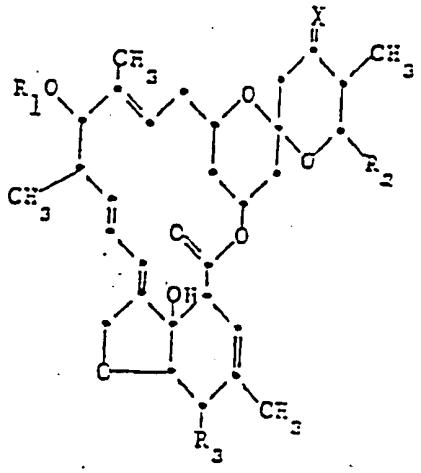
5. Verfahren zur Bekämpfung von Pflanzennematoden, besagtes Verfahren dadurch gekennzeichnet, daß auf die Blätter von Pflanzen, den Boden, in dem diese wachsen, oder auf deren Stiele eine nematizid wirksame Menge der Verbindung, dargestellt durch Strukturformel (I), wie definiert in Anspruch 1, und pharmazeutisch und pharmakologisch verträgliche Salze davon angewendet werden.

6. Zusammensetzung zur Verwendung bei der Behandlung, Prävention oder Bekämpfung von endo- und/oder ektoparasitären Infektionen bei warmblütigen Tieren, besagte Zusammensetzung gekennzeichnet durch eine prophylaktisch, therapeutisch oder pharmazeutisch wirksame Menge der Verbindung, dargestellt durch Strukturformel (I), wie definiert in Anspruch 1, und die pharmazeutisch und pharmakologisch verträglichen Salze davon in einem inerten Feststoff oder flüssigen Träger dafür.

7. Zusammensetzung zur Bekämpfung von Insekten, besagte Zusammensetzung gekennzeichnet durch eine insektizid wirksame Menge der Verbindung, dargestellt durch die Strukturformel (I), wie definiert in Anspruch 1, und die pharmazeutisch und pharmakologisch verträglichen Salze davon und einen inerten Feststoff oder flüssigen Träger dafür.

Patentansprüche für folg nd n Vertragsstaat : ES

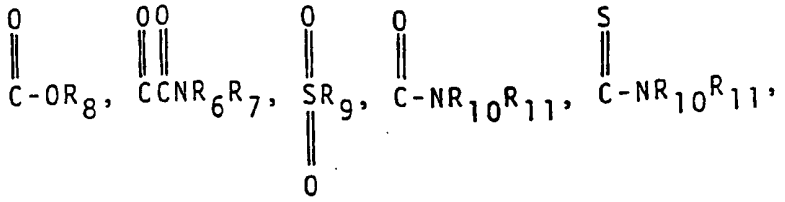
1. Verfahren zur Herstellung von Verbindungen, gekennzeichnet durch die allgemeine Strukturformel (I):



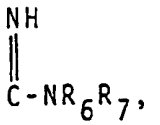
(I)

worin

R_1 4'-(α-L-Oleandrosyl)-α-L-oleandrosyl oder α-L-Oleandrosyl ist; R_2 Isopropyl oder sec-Butyl ist; R_3 Methoxy, Hydroxy, Acetoxy, Methoxyacetoxy oder Chloroacetoxy ist; X NOR_4 oder N-NHR_5 ist; R_4 C_1-C_4-Alkoxymethyl, CH_2COO-Alkyl (C_1-C_4), N-(Allyl)carbamoyl, N-(Propargyl)carbamoyl, Phenylacetyl, substituiert am Phenylring mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, Phenoxyacetyl, wahlweise substituiert am Phenylring mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen oder Benzoyl, wahlweise substituiert mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_5



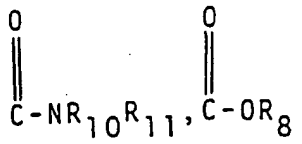
C_1-C_6-Alkanoyl, Formyl, C_1-C_6-Alkyl,



Benzoyl, wahlweise substituiert mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_6 und R_7 Wasserstoff, C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, sind; R_8 C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit ein oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_9 C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist; R_{10} und R_{11} Wasserstoff, C_1-C_6-Alkyl oder Phenyl, wahlweise substituiert mit einem oder zwei Halogenen, C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen oder Nitrogruppen, ist, vorausgesetzt, daß R_{10} und R_{11} nicht gleichzeitig beide Wasserstoff sind; und die pharmazeutisch und pharmakologisch verträglichen Salze davon;

besagtes Verfahren umfassend eine Umwandlung der 23-Keto-(Oxo)-Verbindungen in die Iminoderivate nach Standardmethoden, wobei eine 23-Oxo-Verbindung in Alkohol oder Dioxan in Gegenwart von Essigsäure und einem Überschuß des Amino-Derivatisierungsmittels zusammen mit einer äquivalenten Menge von Natriumacetat bei Raumtemperatur bis 50 °C, gerührt wird, und worin die Verbindungen der Formel (I), wobei X NOR_4 ist und R_4 C_1-C_6-Alkoxycarbonyl, Chloroacetyl, Methoxyacetyl, Phenylacetyl, C_1-C_6-Alkyl-NHCO ist, hergestellt werden durch Behandlung der Verbindungen der Strukturformel (I), worin X NOH ist, mit Säureanhydriden oder Isocyanaten in einem inerten Lösungsmittel in Gegenwart eines tertiären Amins bei einer Temperatur von 0 °C bis Raumtemperatur oder unter Anwendung von Wärme.

2. Verfahren gemäß Anspruch 1, worin R_3 Hydroxy oder Methoxy ist und X, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} und R_{11} wie in besagtem Anspruch 1 sind; worin X N-NHR_5 ist; R_5



oder C_1-C_6 Alkyl ist; R_2 Isopropyl oder sec-Butyl ist; R_3 Hydroxy ist; und R_1, R_8, R_{10} und R_{11} wie in besagtem Anspruch 1 definiert sind.

3. Verfahren zur topischen oder systemischen Bekämpfung von Pflanzeninsekten und zum Schutz von Ernten, Bäumen, Sträuchern, gelagertem Getreide und Zierpflanzen, besagtes Verfahren, dadurch gekennzeichnet, daß eine insektizid wirksame Menge der Verbindung, dargestellt durch Strukturformel (I), wie in Anspruch 1 definiert, und die pharmazeutisch und pharmakologisch verträglichen Salze davon angewendet werden.

4. Verfahren gemäß Anspruch 3, worin in besagter Verbindung X $NOCH_3$ ist; R_2 sec-Butyl ist; R_3 Hydroxy ist; und R_1 4'-(α-L-Oleandrosyl)-α-L-oleandrosyl ist.

5. Verfahren zur Bekämpfung von Pflanzennematoden, besagtes Verfahren dadurch gekennzeichnet, daß auf die Blätter von Pflanzen, den Boden, in dem diese wachsen, oder auf deren Stiele eine nematizid wirksame Menge der Verbindung, dargestellt durch Strukturformel (I), wie definiert in Anspruch 1, und pharmazeutisch und pharmakologisch verträgliche Salze davon angewendet werden.

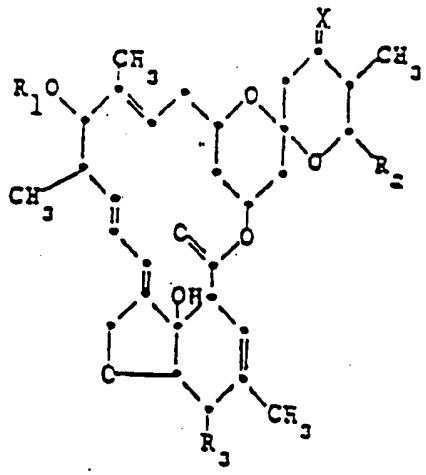
6. Zusammensetzung zur Verwendung bei der Behandlung, Prävention oder Bekämpfung von endo- und/oder ektoparasitären Infektionen bei warmblütigen Tieren, besagte Zusammensetzung gekennzeichnet durch eine prophylaktisch, therapeutisch oder pharmazeutisch wirksame Menge der Verbindung, dargestellt durch Strukturformel (I), wie definiert in Anspruch 1, und die pharmazeutisch und pharmakologisch verträglichen Salze davon in einem inerten Feststoff oder flüssigen Träger dafür.

7. Zusammensetzung zur Bekämpfung von Insekten, besagte Zusammensetzung gekennzeichnet durch eine insektizid wirksame Menge der Verbindung, dargestellt durch die Strukturformel (I), wie definiert in Anspruch 1, und die pharmazeutisch und pharmakologisch verträglichen Salze davon und einen inerten Feststoff oder flüssigen Träger dafür.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, FR, GB, GR, IT, LU, NL, SE

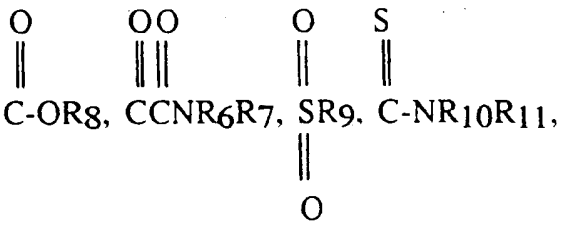
1. Composés caractérisés par la formule développée (I) :



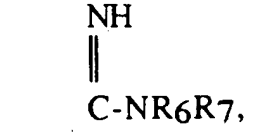
(I)

dans laquelle,

R_1 est un 4'-(α-L-oléandrosyl)-α-L-oléandrosyle ou un α-L-oléandrosyle ; R_2 est un isopropyle ou un sec-butyle ; R_3 est un méthoxy, un hydroxy, un acétoxy, un méthoxyacétoxy ou un chloroacétoxy ; X est NOR_4 ou $N\text{-}NHR_5$; R_4 est un alcoxyméthyle C_1-C_4, CH_2COO-alkyle (C_1-C_4), un N-(allyl)-carbamoyle, un N-(propargyl)carbamoyle, un phénylacétyle substitué sur le noyau phényle par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro, un phénoxyacétyle éventuellement substitué sur le noyau phényle par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro, ou un benzoyle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_5 est

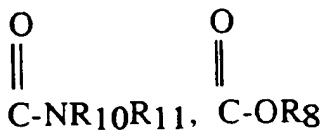


un alcanoyle C_1-C_6, un alkyle C_1-C_6,



un benzoyle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_6 et R_7 sont des atomes d'hydrogène, des alkyles C_1-C_6, ou un phényle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_8 est un alkyle C_1-C_6, ou un phényle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_9 est un alkyle C_1-C_6, ou un phényle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_{10} et R_{11} sont des atomes d'hydrogène, des alkyles C_1-C_6, ou des phényles éventuellement substitués par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro, à la condition que R_{10} et R_{11} ne soient pas des atomes d'hydrogène en même temps ; et les sels acceptables du point de vue pharmaceutique et pharmacologique de ceux-ci.

2. Composé selon la revendication 1, dans lequel R_3 est un hydroxy ou un méthoxy et X, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, et R_{11} sont comme décrits dans ladite revendication 1 ; dans lequel X est N-NHR$_5$;R_5 est



ou un alkyle C_1-C_6 ; R_2 est un isopropyle ou sec-butyle ; R_3 est un hydroxy ; et R_1, R_8, R_{10}, et R_{11} comme défini dans ladite revendication 1.

3. Procédé pour le contrôle des insectes des plantes par voie topique ou systémique, et la protection des plantes agronomiques, des arbres, des buissons, des grains stockés et des plantes ornementales, ledit procédé étant caractérisé par : l'application d'une quantité efficace en tant qu'insecticide du composé représenté par la formule (I), comme défini dans la revendication 1, et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci.

4. Procédé selon la revendication 3, dans lequel, dans ledit composé, X est $NOCH_3$; R_2 est un sec-butyle ; R_3 est un hydroxy; et R_1 est un 4'-(α-L-oléandrosyl)-α-L-oléandrosyle.

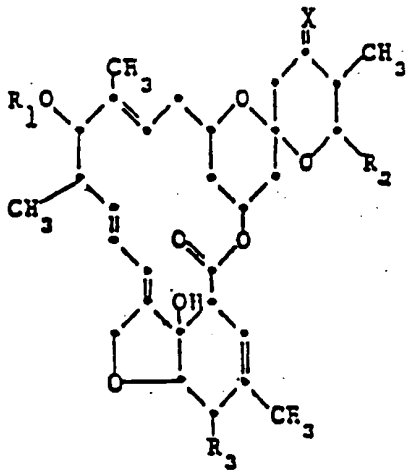
5. Procédé pour le contrôle de nématodes des plantes, ledit procédé étant caractérisé par : application sur le feuillage des plantes, le sol dans lequel elles sont cultivées ou dans le tronc de celles-ci, d'une quantité efficace en tant que nématicide du composé représenté par la formule développée (I) telle que définie dans la revendication 1, et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci.

6. Composition pour une utilisation, dans le traitement, la prévention ou le contrôle d'infections endo- et/ou ectoparasitaires chez les animaux à sang chaud, ladite composition étant caractérisée par : une quantité efficace du point de vue prophylactique, thérapeutique ou pharmaceutique du composé représenté par la formule développée (I) telle que définie dans la revendication 1 et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci ; et un vecteur inerte solide ou liquide de celui-ci.

7. Composition pour le contrôle des insectes, ladite composition étant caractérisée par : une quantité efficace en tant qu'insecticide du composé représenté par la formule développée (I) comme défini dans la revendication 1 et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci ; et un vecteur inerte solide ou liquide de celui-ci.

Revendications pour l'Etat contractant suivant : ES

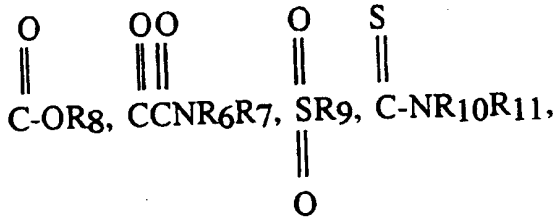
1. Procédés de préparation des composés caractérisés par la formule développée (I) :

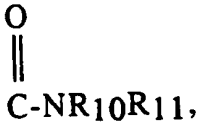


(I)

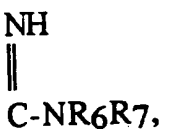
dans laquelle,

R_1 est un 4'-(α-L-oléandrosyl)-α-L-oléandrosyle ou un α-L-oléandrosyle ; R_2 est un isopropyle ou un sec-butyle ; R_3 est un méthoxy, un hydroxy, un acétoxy, un méthoxyacétoxy ou un chloroacétoxy ; X est NOR_4 ou $N\text{-}NHR_5$; R_4 est un alcoxyméthyle C_1-C_4, CH_2COO-alkyle (C_1-C_4), un N-(allyl)-carbamoyle, un N-(propargyl)carbamoyle, un phénylacétyle substitué sur le noyau phényle par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro, un phénoxyacétyle éventuellement substitué sur le noyau phényle par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro, ou un benzoyle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_5 est



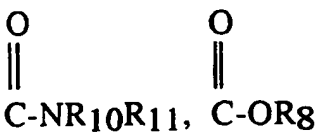


un alcanoyle C_1-C_6, un alkyle C_1-C_6,



un benzoyle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_6 et R_7 sont des atomes d'hydrogène, des alkyles C_1-C_6, ou un phényle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_8 est un alkyle C_1-C_6, ou un phényle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_9 est un alkyle C_1-C_6, ou un phényle éventuellement substitué par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro ; R_{10} et R_{11} sont des atomes d'hydrogène, des alkyles C_1-C_6, ou des phényles éventuellement substitués par un ou deux halogènes, des groupes alkyles C_1-C_4, des groupes alcoxy C_1-C_4 ou des groupes nitro, à la condition que R_{10} et R_{11} ne soient pas des atomes d'hydrogène en même temps ; et les sels acceptables du point de vue pharmaceutique et pharmacologique de ceux-ci, ledit procédé comprenant une conversion de composés 23-céto (oxo) en dérivés imino par des techniques standard, dans lesquelles un composé 23-oxo est mélangé dans de l'alcool ou du dioxane en présence d'acide acétique et d'un excès de dérivé amino avec une quantité équivalente d'acétate de sodium, à une température comprise entre la température ambiante et 50°C, et dans lequel les composés de structure (I) dans laquelle X est NOR_4 et R_4 est un alcoxycarbonyle C_1-C_6, un chloroacétyle, un méthoxyacétyle, un phénylacétyle, un alkyl-NHCO en C_1-C_6, sont préparés par traitement des composés de structure (I), dans lesquels X est NOH, avec des anhydrides acides ou des isocyanates dans un solvant inerte en présence d'une amine tertiaire à une température comprise entre 0°C et la température ambiante ou avec application de chaleur.

2. Procédé selon la revendication 1, dans lequel R_3 est un hydroxy ou méthoxy et X, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, et R_{11} sont comme décrits dans ladite revendication 1 ; dans lequel X est N-NHR_5 ;R_5 est



ou un alkyle C_1-C_6 ; R_2 est un isopropyle ou un sec-butyle ; R_3 est un hydroxy ; et R_1, R_8, R_{10}, et R_{11} sont comme défini dans ladite revendication 1.

3. Procédé pour le contrôle des insectes des plantes par voie topique ou systémique, et la protection des plantes agronomiques, des arbres, des buissons, des grains stockés et des plantes ornementales, ledit procédé étant caractérisé par : l'application d'une quantité efficace en tant qu'insecticide du composé représenté par la formule (I), comme défini dans la revendication 1, et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci.

4. Procédé selon la revendication 3, dans lequel, dans ledit composé, X est $NOCH_3$; R_2 est un sec-butyle ; R_3 est un hydroxy; et R_1 est un 4'-(α-L-oléandrosyl)-α-L-oléandrosyle.

5. Procédé pour le contrôle de nématodes des plantes, ledit procédé étant caractérisé par : application sur le feuillage des plantes, le sol dans lequel elles sont cultivées ou dans le tronc de celles-ci, d'une quantité efficace en tant que nématicide du composé représenté par la formule développée (I) telle que définie dans la revendication 1, et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci.

6. Composition pour une utilisation dans le traitement, la prévention ou le contrôle d'infections endo- et/ou ectoparasitaires chez les animaux à sang chaud, ladite composition étant caractérisée par : une quantité efficace du point de vue prophylactique, thérapeutique ou pharmaceutique du composé représenté par la formule développée (I) telle que définie dans la revendication 1 et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci ; et un vecteur inerte solide ou liquide de celui-ci.

7. Composition pour le contrôle des insectes, ladite composition étant caractérisée par : une quantité efficace en tant qu'insecticide du composé représenté par la formule développée (I) comme défini dans

la revendication 1 et les sels acceptables du point de vue pharmaceutique et pharmacologique de celui-ci ; et un vecteur inerte solide ou liquide de celui-ci.